



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C12N 15/82, 15/29, C07K 14/415, A01H 5/00		A1	(11) International Publication Number: WO 00/11196
			(43) International Publication Date: 2 March 2000 (02.03.00)
<p>(21) International Application Number: PCT/GB99/02720</p> <p>(22) International Filing Date: 17 August 1999 (17.08.99)</p> <p>(30) Priority Data: 9818003.7 18 August 1998 (18.08.98) GB</p> <p>(71) Applicant (for all designated States except US): ZENECA LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): EVANS, Ian, Jeffrey [GB/GB]; Jealott's Hill Research Station, Bracknell, Berkshire RG42 6ET (GB). RAY, John, Anthony [GB/GB]; Jealott's Hill Research Station, Bracknell, Berkshire RG42 6ET (GB).</p> <p>(74) Agents: HUSKISSON, Frank, Mackie et al.; Zeneca Agrochemicals, Intellectual Property Dept., Jealott's Hill Research Station, P.O. Box 3538, Bracknell RG42 6YA (GB).</p>		<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>	
(54) Title: POLYNUCLEOTIDE SEQUENCES			
(57) Abstract			
<p>Nucleotide sequences and the expression products thereof are described for use in the production of transgenic plants. In particular polynucleotides comprising a sequence selected from those depicted in SEQ ID No.1, SEQ ID No.2, SEQ ID No.3, SEQ ID No.4 and SEQ ID No.5 are provided.</p>			

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/02720

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/82 C12N15/29 C07K14/415 A01H5/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C07K A01H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 93 05153 A (ICI PLC) 18 March 1993 (1993-03-18) cited in the application the whole document ---	1-19
A	WO 94 16076 A (DUBOCK ADRIAN CHRISTOPHER ; POWELL KEITH ADRIAN (GB); ZENECA LTD (G) 21 July 1994 (1994-07-21) the whole document ---	1-19
A	DOMON, C., ET AL. : "nucleotide sequence of two anther-specific cDNAs from sunflower (Helianthus annuus L.)" PLANT MOLECULAR BIOLOGY, vol. 15, 1990, pages 643-646, XP002125194 the whole document --- -/--	1-19



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

17 December 1999

Date of mailing of the international search report

11.01.00

Name and mailing address of the ISA

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Authorized officer

Holtorf, S

INTERNATIONAL SEARCH REPORT

International Application No

PCT, 93 99/02720

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>EVARD, J-L., ET AL.: "anther-specific, developmentally regulated expression of genes encoding a new class of proline-rich proteins in sunflower"</p> <p>PLANT MOLECULAR BIOLOGY, vol. 16, 1991, pages 271-281, XP002125195 the whole document</p> <p>-----</p>	1-19

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 99/ 02720

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-19 partially

Nucleotide sequence as depicted in SEQID 1, different fragments thereof and translation products of said sequences; furthermore, a method to produce transgenic plants expressing said nucleotide sequences.

2. Claims: 1-19 partially

Nucleotide sequence as depicted in SEQID 2, different fragments thereof and translation products of said sequences; furthermore, a method to produce transgenic plants expressing said nucleotide sequences.

3. Claims: 1-19 partially

Nucleotide sequence as depicted in SEQID 3, different fragments thereof and translation products of said sequences; furthermore, a method to produce transgenic plants expressing said nucleotide sequences.

4. Claims: 1-19 partially

Nucleotide sequence as depicted in SEQID 4, different fragments thereof and translation products of said sequences; furthermore, a method to produce transgenic plants expressing said nucleotide sequences.

5. Claims: 1-15,17,19

Nucleotide sequence as depicted in SEQID 5, different fragments thereof and translation products of said sequences; furthermore, a method to produce transgenic plants expressing said nucleotide sequences.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 99/02720

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9305153 A	18-03-1993	AU 667825 B	18-04-1996
		AU 2480892 A	05-04-1993
		BR 9206420 A	30-05-1995
		CA 2116541 A	18-03-1993
		EP 0603216 A	29-06-1994
		JP 6510197 T	17-11-1994
		NZ 244091 A	26-10-1994
		US 5538525 A	23-07-1996
		US 5689043 A	18-11-1997
		US 5824869 A	20-10-1998
WO 9416076 A	21-07-1994	AU 5820494 A	15-08-1994

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

HUSKISSON, Frank, Mackie
Syngenta Limited
Intellectual Property Dept.
Jealott's Hill Research Station
P.O. Box 3538
Bracknell RG42 6YA
ROYAUME-UNI

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Date of mailing (day month year) 12 April 2001 (12.04.01)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference PPD 50355/WO	
International application No. PCT/GB99/02720	International filing date (day/month/year) 17 August 1999 (17.08.99)

1. The following indications appeared on record concerning:		
<input checked="" type="checkbox"/> the applicant	<input type="checkbox"/> the inventor	<input type="checkbox"/> the agent <input type="checkbox"/> the common representative
Name and Address ZENECA LIMITED 15 Stanhope Gate London W1Y 6LN United Kingdom	State of Nationality GB	State of Residence GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	
2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:		
<input type="checkbox"/> the person	<input checked="" type="checkbox"/> the name	<input checked="" type="checkbox"/> the address <input type="checkbox"/> the nationality <input type="checkbox"/> the residence
Name and Address SYNGENTA LIMITED Fernhurst Haslemere Surrey GU27 3JE United Kingdom	State of Nationality GB	State of Residence GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	
3. Further observations, if necessary: This is only a change of name and address, and no transfer of patent or other rights has occurred. Agent's address has also been changed accordingly.		
4. A copy of this notification has been sent to:		
<input checked="" type="checkbox"/> the receiving Office	<input type="checkbox"/> the designated Offices concerned	
<input type="checkbox"/> the International Searching Authority	<input checked="" type="checkbox"/> the elected Offices concerned	
<input type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:	

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer S. Buttay Telephone No.: (41-22) 338.83.38
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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

15

Applicant's or agent's file reference PPD 50355/WO	FOR FURTHER ACTION		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB99/02720	International filing date (day/month/year) 17/08/1999	Priority date (day/month/year) 18/08/1998	
International Patent Classification (IPC) or national classification and IPC C12N15/29			
Applicant ZENECA LIMITED et al.			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 8 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 18/11/1999	Date of completion of this report 23.11.2000
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Page, M Telephone No. +49 89 2399 7322 

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/02720

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:

Description, pages:

1-28 as originally filed

Claims, No.:

1-19 as originally filed

Drawings, sheets:

1/19-19/19 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/02720

☐ the drawings. sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:
see separate sheet

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-5, 7-15, 18
	No:	Claims	6, 16, 17, 19
Inventive step (IS)	Yes:	Claims	1-4
	No:	Claims	5-19
Industrial applicability (IA)	Yes:	Claims	1-19
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/02720

Re Item I

Basis of the report

The examination is being carried out on the **following application documents**:

Text for the Contracting States:

AT BE CH DE DK ES FI FR GB GR IT IE LI LU MC NL PT SE

Description, pages:

1-28 as originally filed

Claims, No.:

1-19 as originally filed

Drawings, sheets:

1/19-19/19 as originally filed

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1) Reference is made to the following documents:

- D1: WO 93 05153 A (ICI PLC) 18 March 1993 (1993-03-18) cited in the application
- D2: WO 94 16076 A (DUBOCK ADRIAN CHRISTOPHER ;POWELL KEITH ADRIAN (GB); ZENECA LTD (G) 21 July 1994 (1994-07-21)
- D3: DOMON,C., ET AL. : 'nucleotide sequence of two anther-specific cDNAs from sunflower (Helianthus annuus L.)' PLANT MOLECULAR BIOLOGY, vol. 15, 1990, pages 643-646, XP002125194

2) Novelty - Art.33(1) and (2) PCT:

- 2.1 Claims 1-4 can be considered novel as the sequences listed are new.
- 2.2 Claim 5 is now acknowledged as demonstrating novelty over the prior art. See, however, Item VIII a) below.
- 2.3 Claim 6 cannot be considered new in the light of D2. The applicant uses the same arguments regarding the novelty of claim 6 over D2 as for claim 5. The polynucleotide sequences of claim 6, however, are considerably shorter, and it is maintained that SEQ ID 27 of D2 will indeed hybridise to SEQ ID NOs. 2 and 3 of the present application. The area of homology between the Cb-AMP2 gene (*supra*) and SEQ ID No. 2 lies between bp 95 and bp 244 and between the Cb-AMP2 gene and SEQ ID No. 3 lies between bp 109 and bp 197. See also VIII a) below.
- 2.4 Claim 7 can be regarded as being novel in the light of the prior art, as none of the known documents propose modifying the polynucleotide sequence to encode signal peptides.
- 2.5 Claims 8, 10-15 and 18 are also now considered to be novel in the light of the prior art. Although D2 discloses polynucleotide sequences falling within the scope of claim 6, the specific modifications and uses of such sequences put forth in the said claims are not disclosed therein.
- 2.6 Claim 9 appears to be new in the light of the prior art, as none of the known documents disclose polynucleotide sequences modified in such a fashion. See also VIII c) below.
- 2.7 Claims 16-17 cannot be acknowledged as being new in light of the prior art. Documents D1 and D3 disclose proteins that are regarded as being "similar" to those of the present application. See also VIII b) below.
- 2.8 Claim 19 is not new in the light of D2. Polypeptides expressed from polynucleotide sequences falling within the scope of claim 6 have previously been produced in microorganisms (D2 page 3 paragraph 5 - page 4 paragraph 1).

3) Inventive Step - Art.33(1) and (3) PCT:

- 3.1 The following comments on inventive step are confined to subject matter which could be acknowledged as being novel.

The closest prior art document is D1, which discloses the polypeptide and polynucleotide sequences of a number of plant antimicrobial proteins (AMP's), including two from *Dahlia merckii* (*D. merckii*). The document further goes on to disclose the use of these proteins in combatting microbial infection in a broader range of plants, either by the use of (a) recombinant AMP protein(s) or by producing plants transgenic with regard to their genes, which are then inherently resistant to such infection (D1 page 3 lines 24-34 and claims 24, 29, 33 and 35). As these plants are also transgenic with respect of these sequences it is given that they are stably incorporated into the genome and inheritable (D1 page 9 lines 24-5).

The current application identifies and seeks protection for five further members of the AMP family identified from *D. merckii*.

The technical problem to be solved is the development of further antimicrobial strategies in plants using the AMP family of proteins and their respective genes.

- 3.2 Claims 1-4 appear to be inventive in the light of the prior art. Although *D. merckii* AMP polynucleotide and polypeptide sequences are known, the applicant's argument that there would be no motivation to look for further similar sequences within the same species is accepted.
- 3.3 Claim 5 cannot be considered as being inventive. Although it has been acknowledged that there was no reasonable expectation of success in isolating further antimicrobial polynucleotide and polypeptide sequences from *D. merckii*, it is to be expected that such sequences exist in other plant species, as witnessed by the presence of these genes in a wide variety of species, such as *Raphanus*, *Brassica*, *Arabidopsis*, *Cnicus*, *Lathyrus* and *Clitoria* (D1 page 3). The claimed subject matter is therefore obvious to the skilled artisan.
- 3.4 Claims 7 and 8 cannot be considered inventive as the use of organelle specific signal peptides and translation-enhancing promoters for known or obvious proteins

is a routine matter to one skilled in the art. It cannot be seen where an inventive step might lie.

3.5 Claim 9 cannot be considered inventive as such alterations to the codons of obvious polynucleotide sequences is obvious to one skilled in the art. It cannot be seen where an inventive step might lie.

3.6 Claims 10-15 cannot be considered inventive in the light of D1 or D2. These documents disclose the insertion of polynucleotide sequences encoding antimicrobial proteins into a vector for transformation of plant tissue so that the said tissue produces the said proteins (D1 page 3 lines 25 and 29, D2 page 4 §1). Thus the subject matter of the claims is routine for obvious polynucleotide sequences.

3.7 Claim 18 cannot be considered inventive in the light of D1 or D2, wherein methods are disclosed for using microorganisms for producing the claimed protein *in situ* (D1 page 7 line 31-page 8 line 11, D2 page 4 §3). In the light of these documents, it cannot be seen where an inventive step might lie.

Note: Had the sequences and methods of claims 7-18 been restricted in their scope to the subject matter of claims 1-4, it would also have been possible to acknowledge inventive step for these claims. However, the dependency on obvious subject matter (claims 5 and 6) means that the dependent claims are also obvious, as they all refer to subject matter or procedures that are considered to be routine for the person skilled in the art.

Re Item VII

Certain defects in the international application

- a) Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D2 and D3 are not mentioned in the description, nor are these documents identified therein.

Re Item VIII

Certain observations on the international application

- a) The use of the terms "a protein having substantial similar activity to...", "complementary to one which..." and "still hybridises with a sequence..." in claims 5 and 6 render the scope of the said claims unclear and should therefore be defined. Such formulations are unsuitable for defining the subject matter of claims (Art. 6 PCT).
- b) The use of the terms "95% *similar*" and "85% *similar*" in claims 16 and 17 render the scope of the said claims unclear (Art. 6 PCT). In contrast to the term "identical" (e.g. 95% *identical* to SEQ ID NO. X), the term "similar" has no recognised meaning in this context (see PCT Guidelines CIII-4.2, -4.5 and -4.5a).
- c) The definition of the subject matter falling under claim 9 is not immediately evident to the reader, particularly with regard to the proviso that the proposed polynucleotide sequence encodes a protein that is "substantially the same" and that the homology to the endogenous sequence "is less than about 60%" (Art 6 PCT).